Leishmaniasis Made Ridiculously Simple

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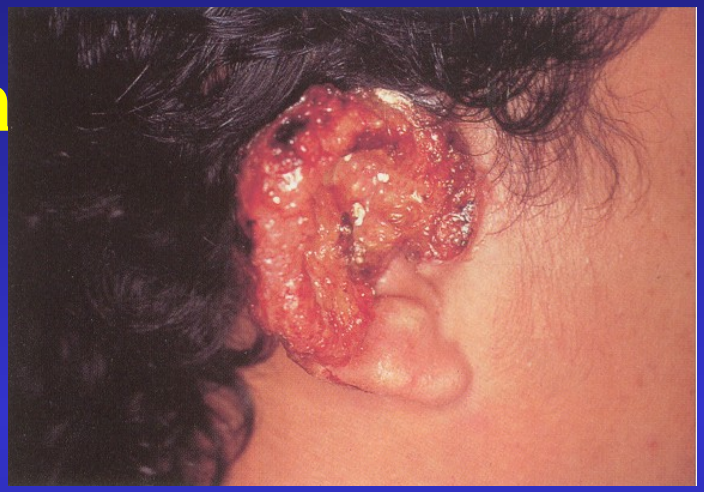
Walter Reed Army Medical

Leishmaniasis

- Protozoal disease
- Cutaneous leishmania
  - Localized cutaneous
  - Diffuse cutaneous
  - Recidivans
  - Post-kala-azar



- Mucocutaneous leishmaniasis
- Visceral leishmaniasis
- Viscerotropic leishmaniasis

Leishmaniasis

- Parasite is found throughout the world
- Transmitted by the bite of female sandflies
- Over twenty different species
  - New World parasites
  - Old World parasites
- Uncommon in the United Stat
- Major epidemics worldwide

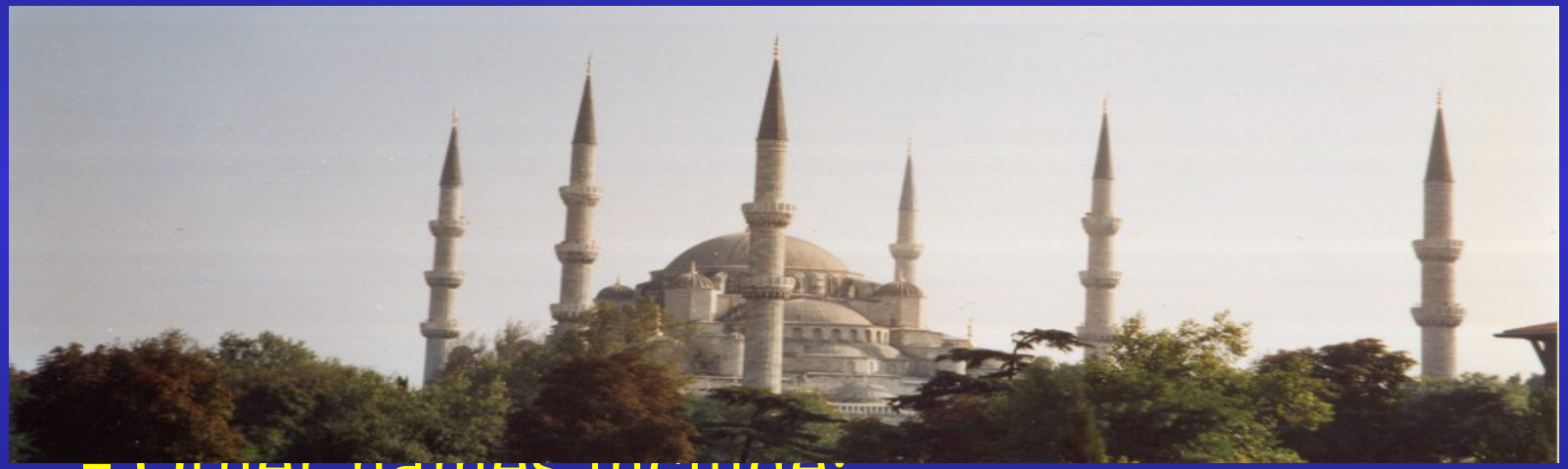
So why are we talking about this?

- Military physicians play a major role
- Incidence is rising worldwide
  - international travel
  - immigration
  - overseas military deployment
  - AIDS
- New clinical manifestations
  - Viscerotropic disease

This is demoralizing to the troops

Background

- Ancient descriptions
- First described in English in 1756
  - “Aleppo evil”



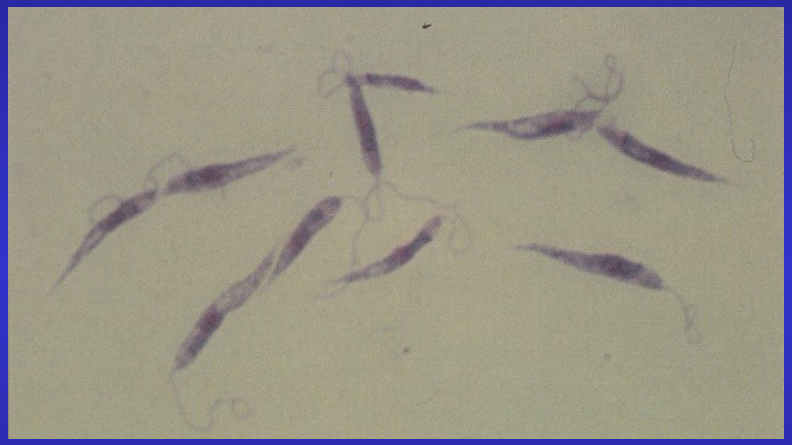
  - Other names include:
    - Delhi boil, Oriental sore, Rose of Jericho, Baghdad sore, Biskra button
    - Espundia, Kala-azar, black fever, dumdum fever

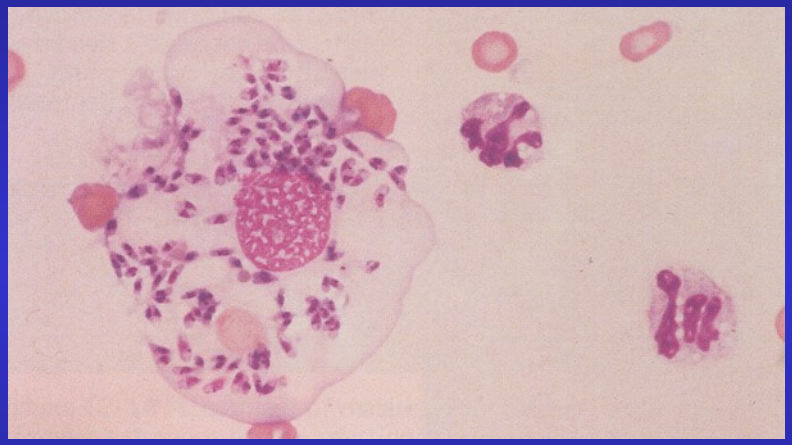
Background

- 1885 - Major D.D. Cunningham observed organisms from “Delhi Boil”
- 1898 - Confirmed by Russian army physician
- 1903 - British military physicians discover parasites in splenic tissue in patients with Dum-Dum Fever.
- Organism named *Leishmania donovani*

Pathophysiology

- Transmitted by sandflies
  - Promastigote stage in the sandfly
  - Amastigote stage in animal and human hosts



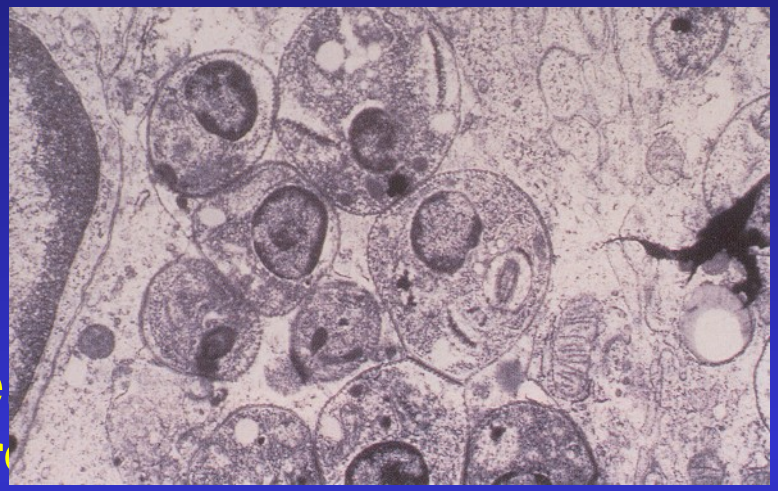


- Amastigotes live in macrophages
- Case reports of transmission through:
  - needle sharing, transfusions, pregnancy and sexual contact

Try to avoid this…

Pathophysiology

- Parasites incubate for weeks to months



- Varied pre
  - immune r
  - species
  - parasite burden
- Tissue damage
- May self heal or progress to chronic disease

Frequency in the U.S.

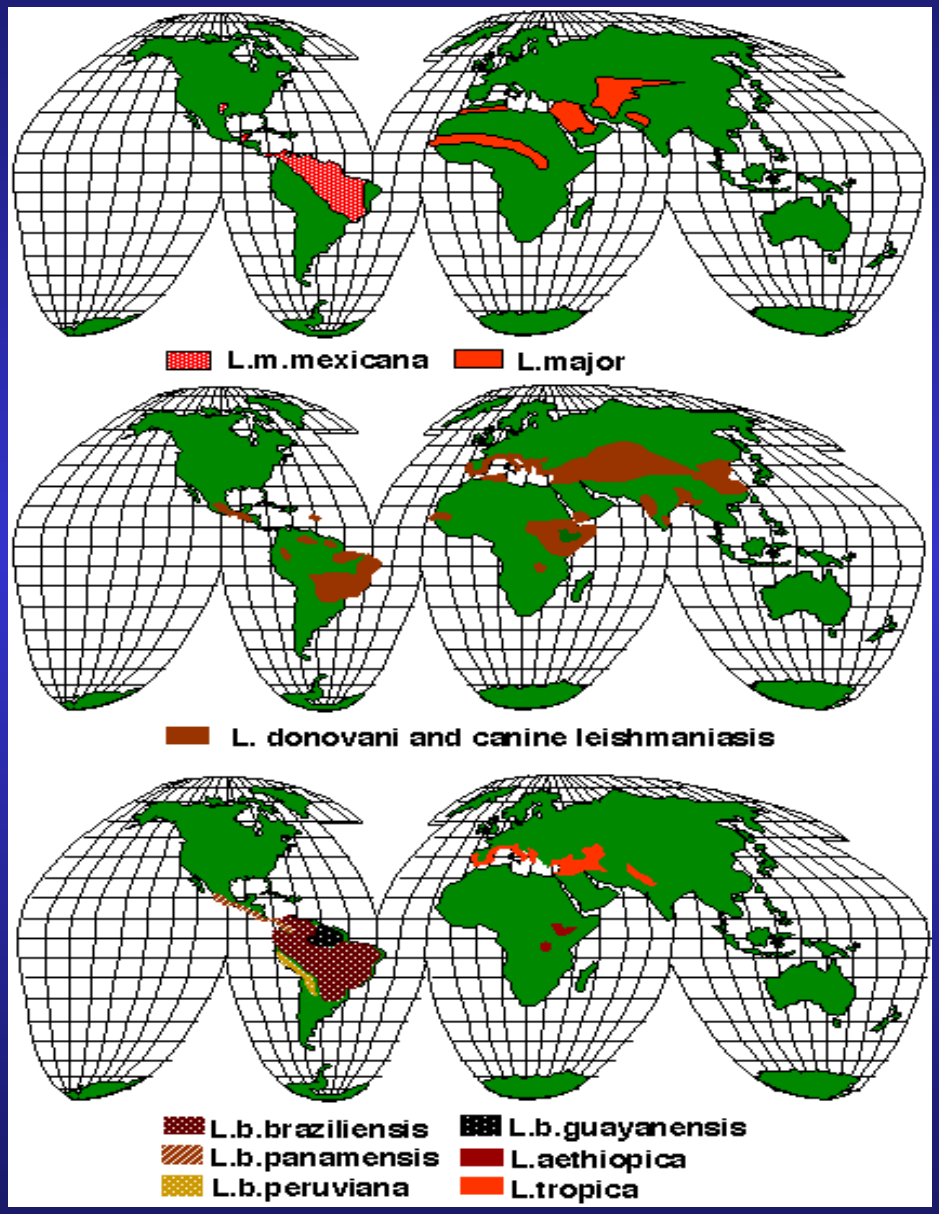
- Uncommon
- Endemic focus in Texas
  - Southern plains woodrat
  - Coyotes and domesticated animals
  - Spread by *Lutzomyia* sandfly
- 450 military personnel
- Persian Gulf War:
  - 20 case of cutaneous disease
  - 12 cases of viscerotropic disease
- CDC reported 129 cases in 5 year period

International Frequency

- Endemic in 82 countries
- 600,000 cases per year
- 12 million infected people
- Visceral leishmaniasis
  - approximately 100,000/year
- Localized cutaneous leishmaniasis
  - 90% come from Afghanistan, Saudi Arabia, Syria, Iran and Brazil

International Frequency

- Old World disease
  - Middle East
  - Indian subcontinent
  - Southwest Asia
  - Mediterranean basin
  - East Africa
  - China
  - republics of the former soviet union
- New World disease
  - throughout the Americas
  - except Canada, Chile and Uruguay



Animal Reservoirs

- Humans are incidental hosts
- Animal reservoir
  - Wild animals
  - Domesticated dogs

Old World

-Domestic & feral dogs
-Rodents
-Foxes
-Jackals
-Wolves
-Raccoon-dogs
-Hyraxes

New World

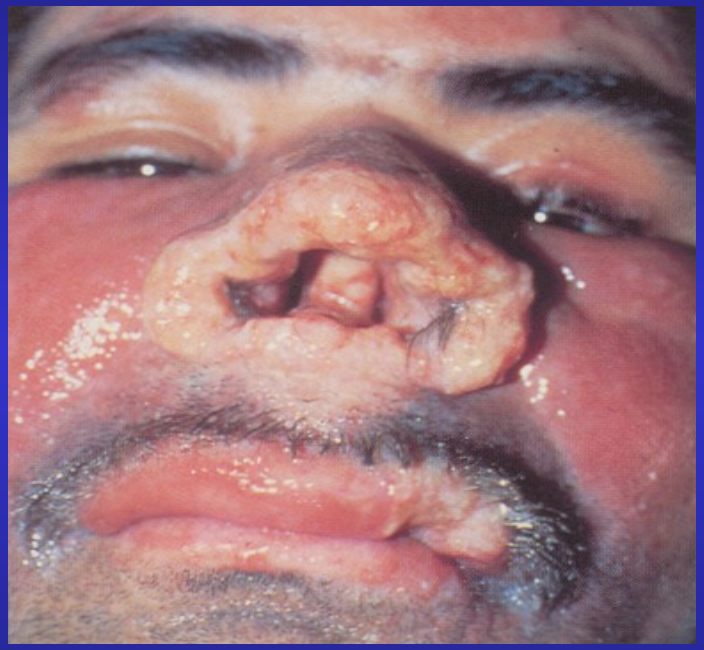
-Sloths
-Anteaters
-Opossums
-Rodents

Human Reservoirs

- Visceral leishmaniasis
  - In India
  - human-sandfly-hum
- Old World *L. tropica*
  - no animal reservoir

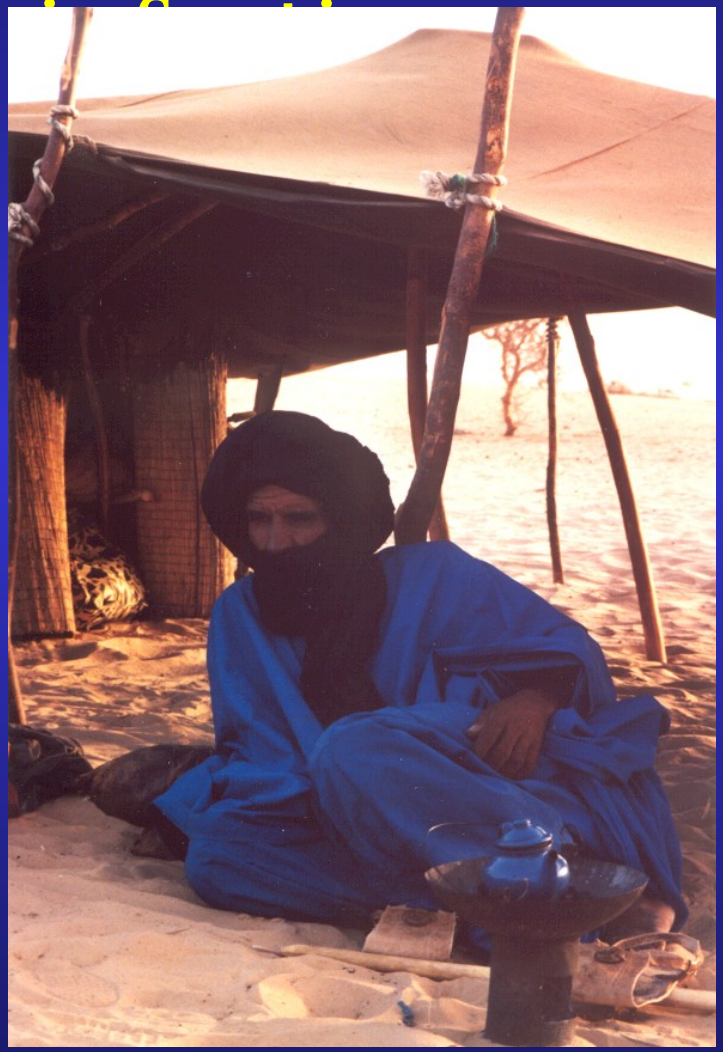
Morbidity/Mortality

- Cutaneous leishmaniasis
  - Localized may resolve
  - May be chronic
  - Low mortality
- Mucocutaneous leishmaniasis
  - Chronic and progressive disease
  - Variable mortality
- Visceral Leishmaniasis
  - Mortality 75-95%
  - With treatment 5% mortality



Epidemiology

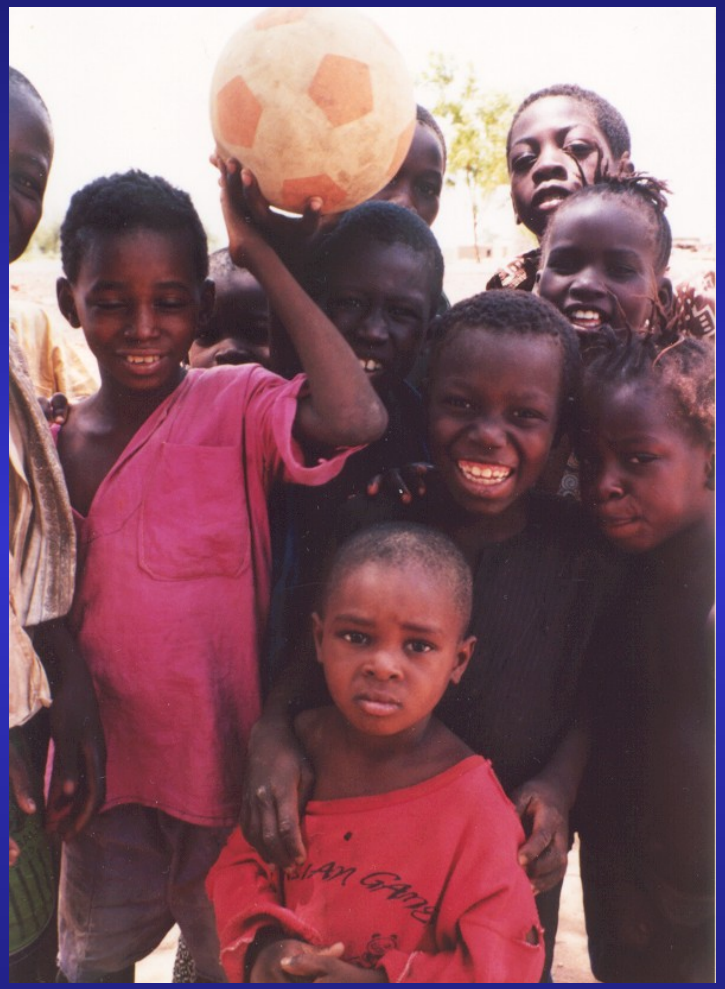
- Males have increased rate of



- Male/female 2:1
- secondary to environmental exposure
  - occupation
  - leisure

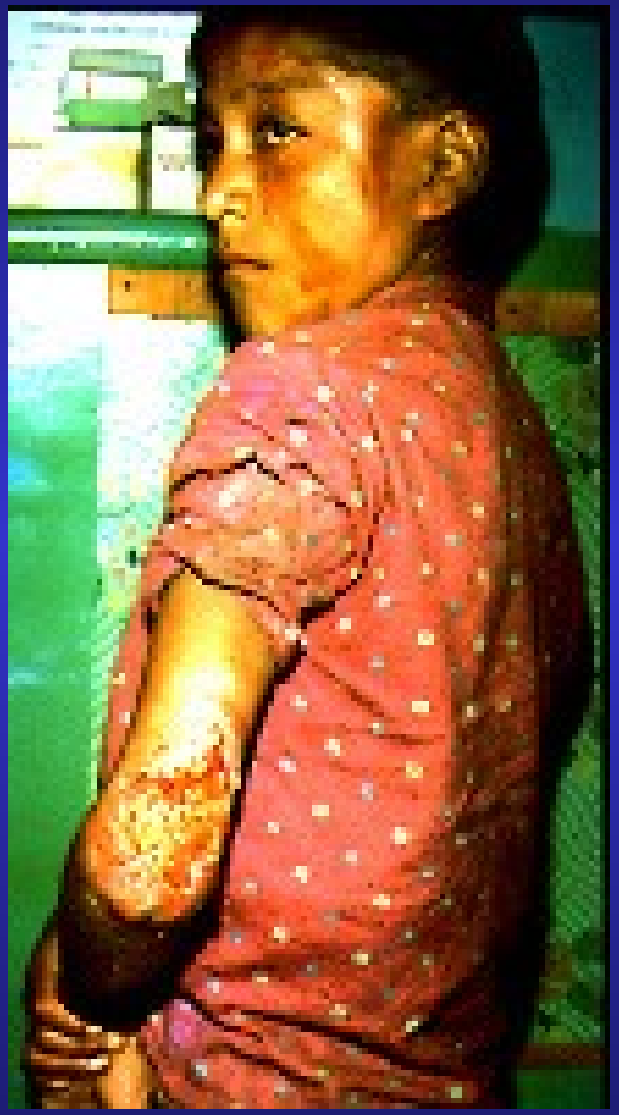
Epidemiology

- Affects various age groups
  - species
  - geographic location
  - disease reservoir
  - host immune status
- Visceral leishmaniasis
  - No animal reservoir
    - All age groups
  - With animal reservoir
    - disease of childhood
- Cutaneous leishmaniasis
  - affects all ages



Localized Cutaneous Leishmaniasis

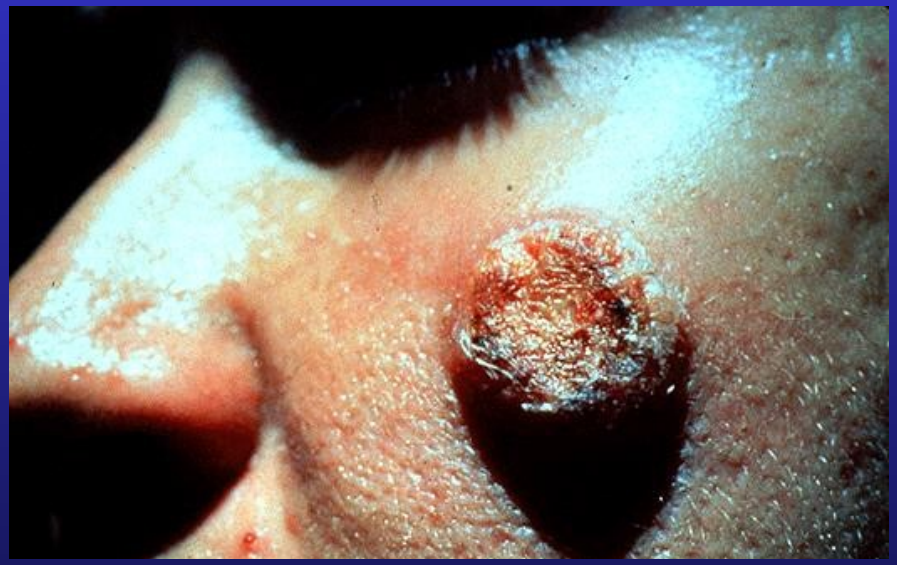
- History
  - Inoculation
  - Incubation
  - Red papule
  - No systemic symptoms
  - Localized lymphangitic spread
  - Secondary infection
  - Spontaneous healing
  - hypopigmented healed lesions
  - New world disease may progress to mucocutaneous disease

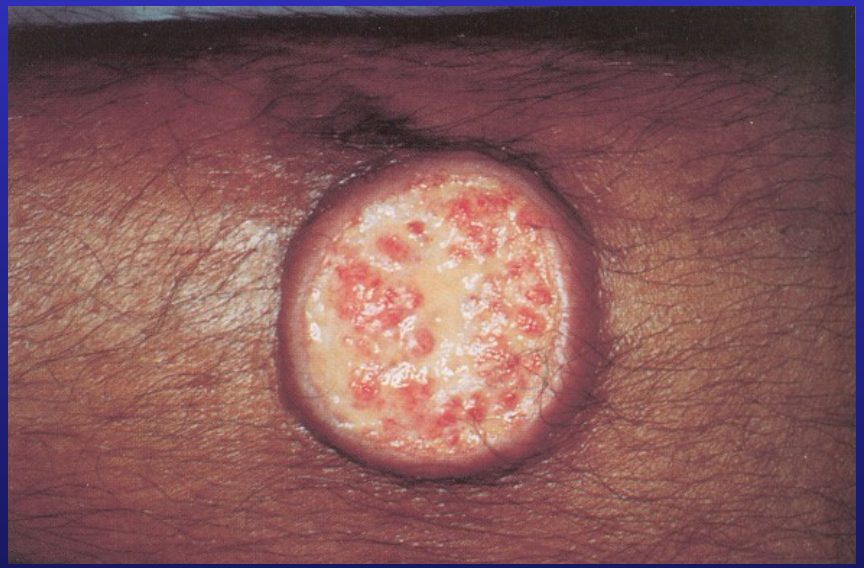


Localized Cutaneous Leishmaniasis

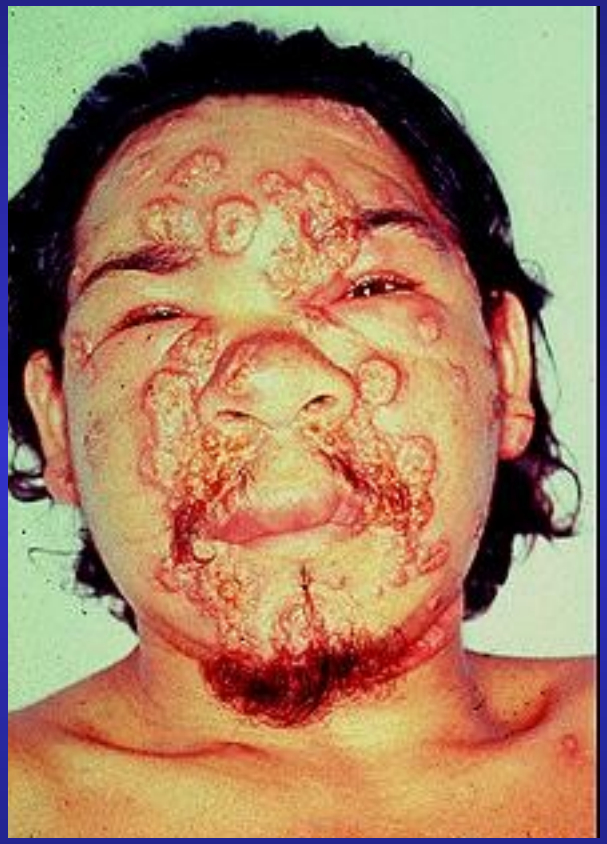
- Physical

- Firm papule with ulceration
- “Volcano sign”
- Fibrotic and hyperkeratotic
- Satellite lesion
- Painless
- Bacterial infection may affect presentation





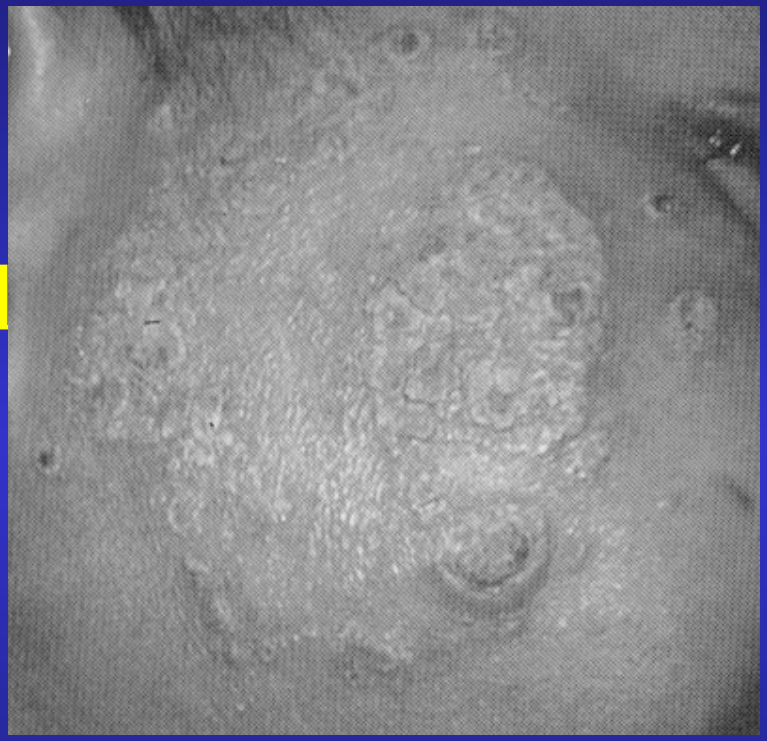
Diffuse Cutaneous Leishmaniasis



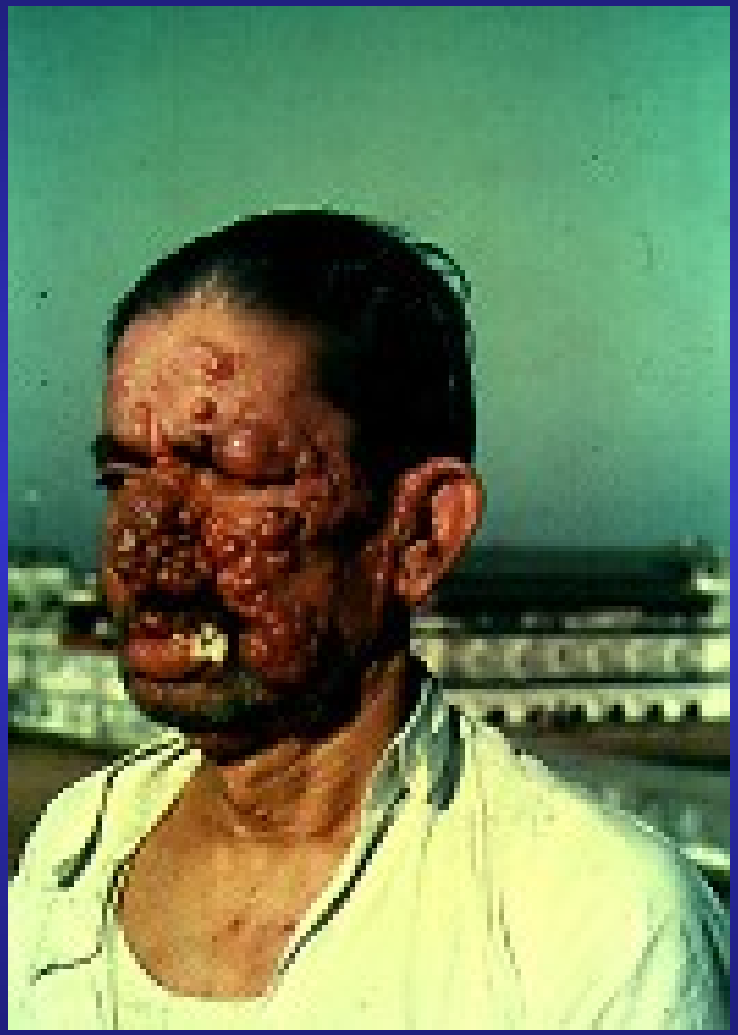
- Anergic hosts
- Initial primary lesion
- Plaques and nodules
- Generally non-ulcerating
- No systemic symptoms
- Chronic
- More common in Central and South America
- May occur in East Africa

Leishmaniasis Recidivans

- Occurs after healing
- Commonly on face
- New lesions form on ed
- Infections from:
  - Reactivation
  - Infection
- Resistant to treatment



Post Kala-Azar Leishmaniasis

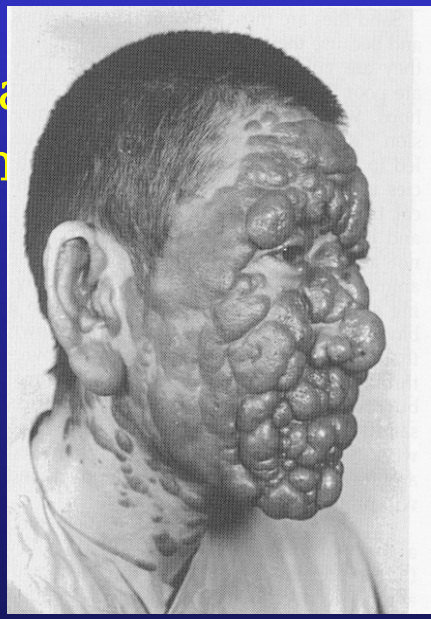


India

- Occurs several years after recovery
- Multiple hypopigmented dermal lesion
- Nontender
- Face and trunk
- Requires intensive treatment

Africa

- Occurs shortly after trea
- Rash on face and extren
- Spontaneous resolution

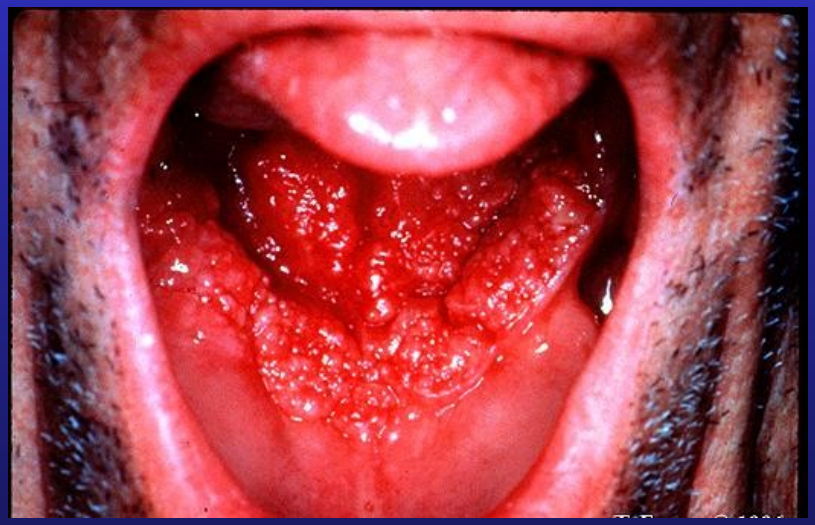


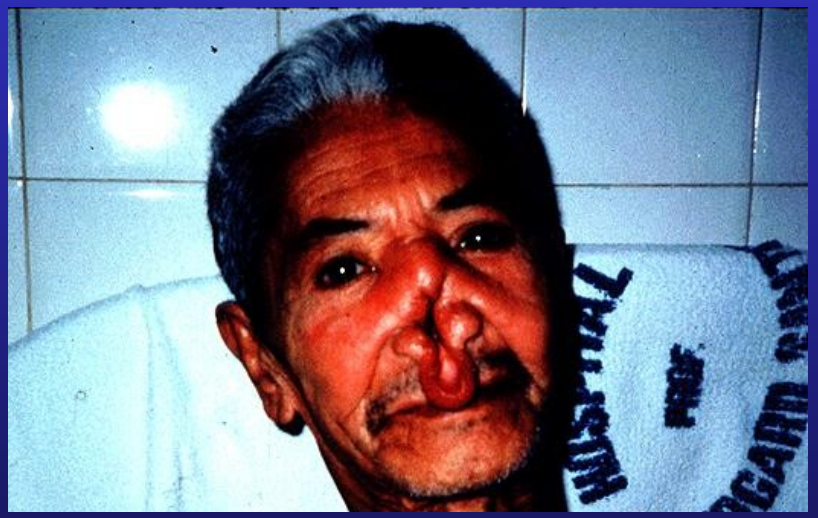
Mucocutaneous Leishmaniasis

- New World *L. braziliensis*
- Old World *L. aethiopica*
- Occurs after healing
- Years later mucosal involvement
- Difficult to treat
- Increased mortality
- May occur after inadequate treatment

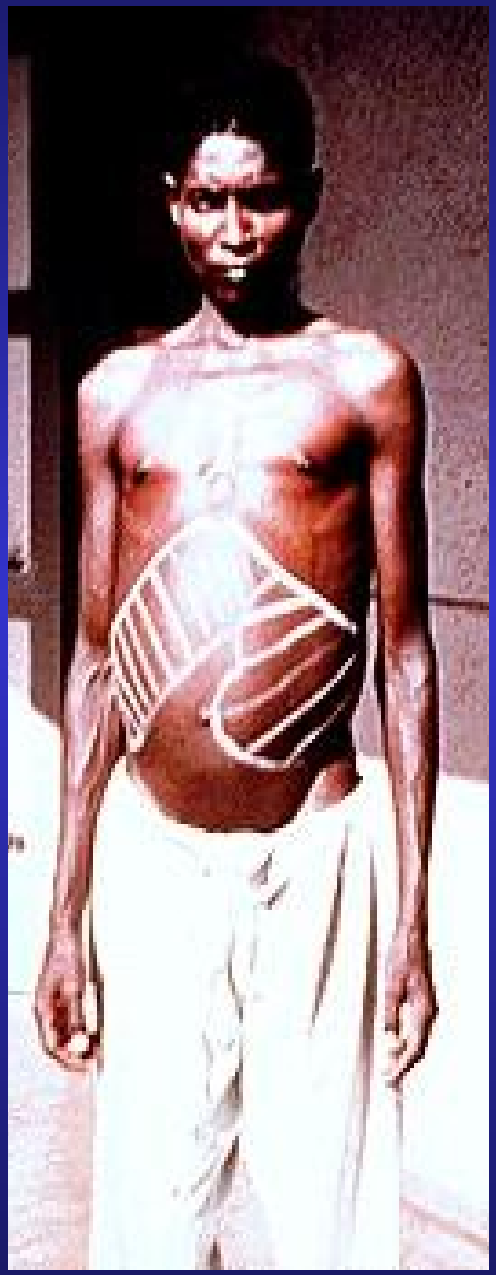
Mucocutaneous Leishmaniasis

- Initial large lesion
- Healed scar
- Initially present with congestion
- Nare abnormalities
- “Parrot beak” or “camel nose”
- Hoarseness
- Suffocation and aspiration pneumonia





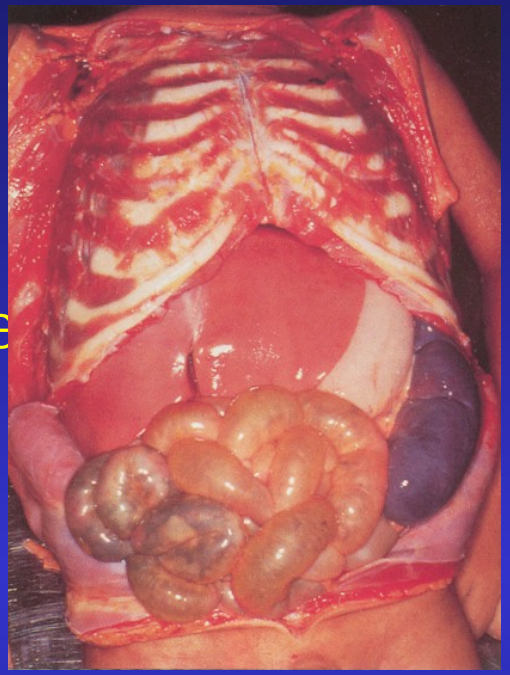
Visceral Leishmaniasis

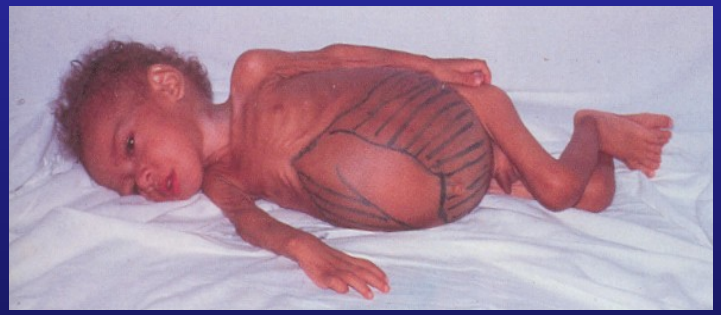


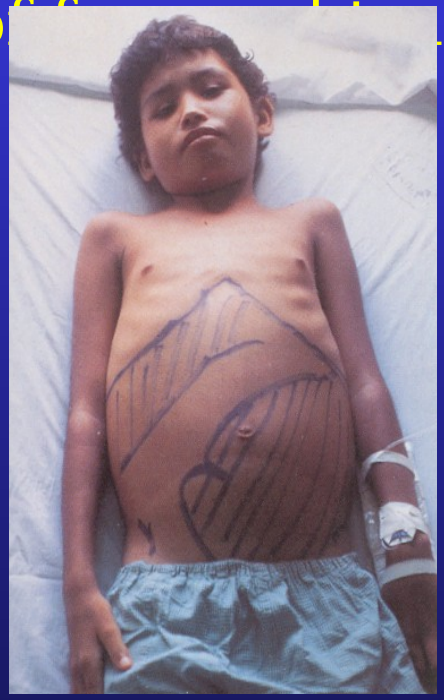
- Fatal
- Systemic infection
- Pentad of disease:
  - fever, weight loss, hepatosplenomegaly, pancytopenia and hypergammaglobulinemia
- Night sweats, anorexia and weakness
- Characteristic skin
- “Black Fever”
- Variable incubation period
- Death from immunosupres
  and secondary infection

Visceral Leishmaniasis

- Physical exam
  - Cachetic patient with abdominal distension
  - Liver and spleen firm and non-tende
  - Epistaxis and petechia
  - Lymphadenopathy
  - Patchy darkening of f nk
  - Complications



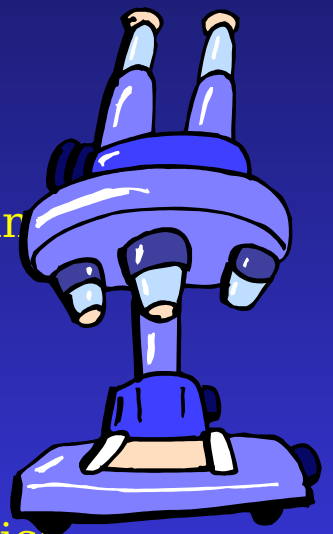




Viscerotropic Leishmaniasis

- Gulf War veterans
- Caused by *L. tropica*
- Incubation 1 month to 2 years
- Presents with nonspecific symptoms

Causes of Cutaneous Leishmaniasis



Localized cutaneous leishmaniasis:

Old World

L.donovani: China, India and Bangladesh.

L. tropica: Middle East, China, India and Mediterranean.

L. major: Middle East, Africa, India, and Asia.

L.aethiopica: Ethiopia, Kenya, and Namibia.

L. infantum: Asia, Africa and Europe.

New World

L. mexicana mexicana: Central, South and North America.

L. mexicana amazonensis: Dominican Republic, Central and South America.

L. mexicana venezuelensis: Venezuela.

L. braziliensis braziliensis: Central and South America.

L. braziliensis guyanensis: Guyana, French Guyana, Surinam and Brazil.

L. braziliensis panamensis: Costa Rica, Panama, Colombia and Ecuador.

L. braziliensis peruviana: Peru and Argentina.

L. donovani chagasi: Texas, Caribbean, Central and South America.

L. shawi: South America

Causes of Cutaneous Leishmaniasis

Diffuse cutaneous leishmaniasis:

Old World

L. aethiopica: Ethiopia, Kenya and Namibia.

New World

L. mexicana mexicana: Central, South and North America.

L. mexicana amazonensis: Dominican Republic, Central/South America.

Leishmaniasis recidivans:

Old World

L. tropica: Middle East, China, India and Mediterranean.

New World

L. braziliensis braziliensis: Central and South America.

Post kala-azar leishmaniasis:

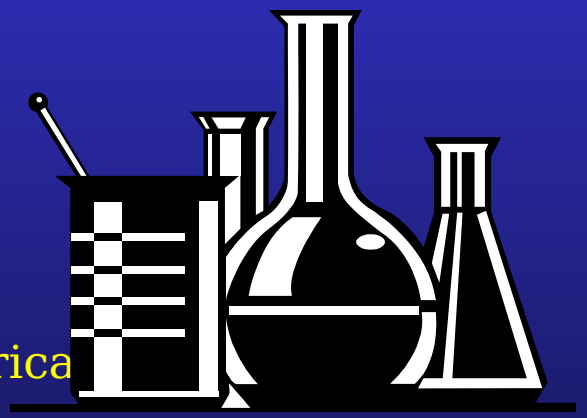
Old World

L. donovani: China, India and Bangladesh.

L. infantum: Asia, Africa and Europe.

New World

L. donovani chagasi: Central and South America



Causes of Mucocutaneous Leishmaniasis

Mucocutaneous leishmaniasis:

- Old World
  - *L. aethiopica*: Ethiopia, Kenya and Namibia
- New World: most often caused by
  - *L. braziliensis braziliensis*: Central and South
  - *L. braziliensis panamensis*: Central and Sout
  - *L. braziliensis guyanensis*: Guyana, Surinam
- Also seen with
  - *L. mexicana mexicana*: Central South and No
  - *L. mexicana amazonensis*: Brazil and Panama

Causes of Visceral Leishmaniasis

Visceral leishmaniasis:

Old World

L. donovani: China, India and Bangladesh.

L. infantum: Asia, Africa and Europe.

New World

L. donovani chagasi: Central and South America

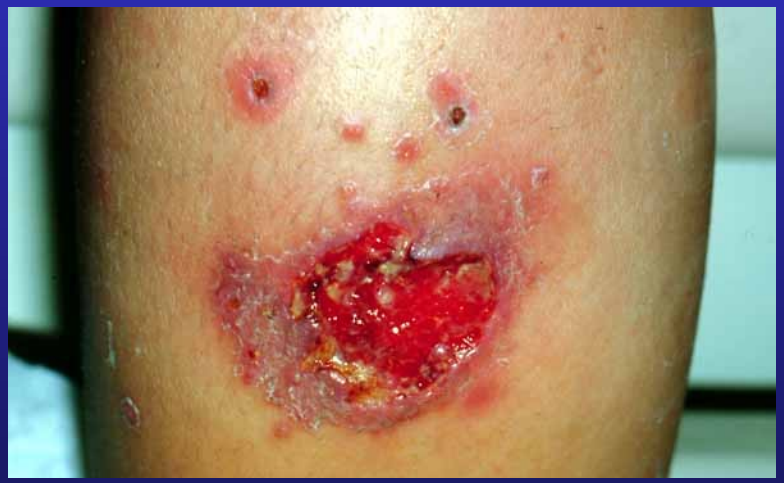
Viscerotropic leishmaniasis:

Old World

L. tropica: Middl

Differential Diagnosis

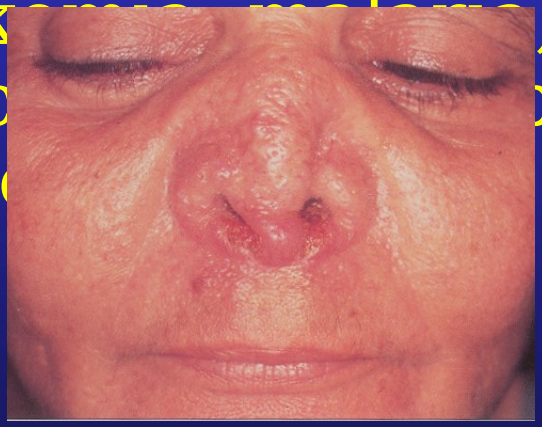
- Cutaneous leishmaniasis:
  - Fungal- paracoccidiomycosis, chromoblastomycosis, sporotrichosis, blastomycosis
  - Bacterial- Mycobacterioses: leprosy, lupus vulgaris, tuberculosis verrucosa cutis, other mycobacterioses
  - Treponematoses- Pinta, yaws, syphilis
  - Staphylococcal/streptococcal pyodermas- impetigo, ecthyma, furunculosis
  - Parasitic- amebiasis, malaria
  - Viral- orf
  - Inflammatory- Sarcoidosis, Foreign body granuloma, pyogenic granuloma
  - Neoplastic- cutaneous T-cell lymphoma, basal cell carcinoma, squamous cell carcinoma, keratoacanthoma, cutaneous metastases
  - Granuloma faciale
  - Jessner's lymphocytic infiltrate
  - Lymphocytoma cutis
  - Discoid lupus erythematosus
  - Psoriasis
  - Keloids

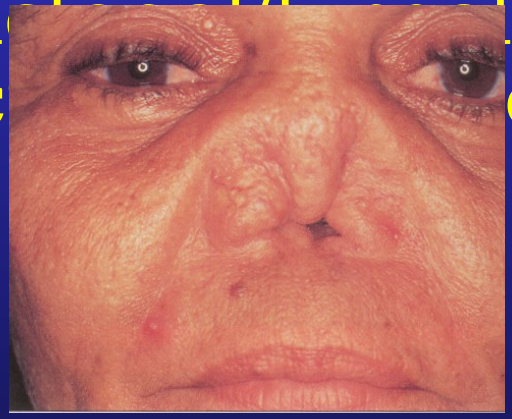


Differential Diagnosis

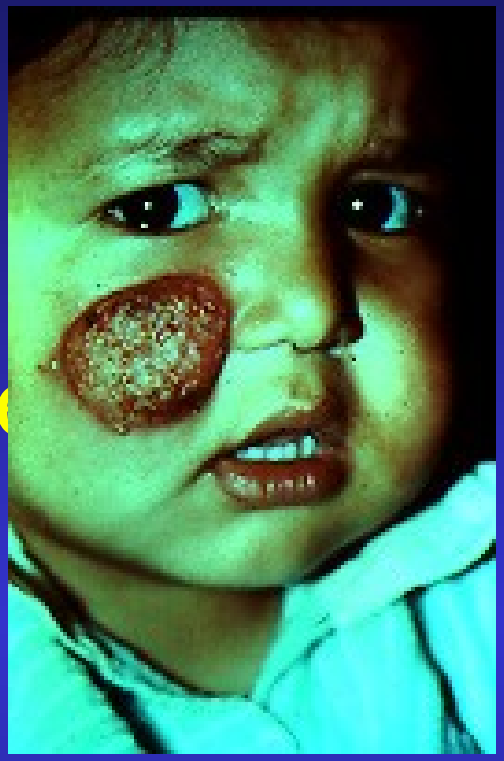
- Mucocutaneous leishmaniasis:
  - Paracoccidiomycosis, sporotrichosis, histoplasmosis, blastomycosis, lethal midline granuloma, carcinoma, tuberculosis, gummatous syphilis, cancrum oris, yaws and rhinoscleroma

- Visceral leishmaniasis:
  - Leuk[illegible], ba[illegible]/viral infec[illegible]erc[illegible]oma and typh[illegible]





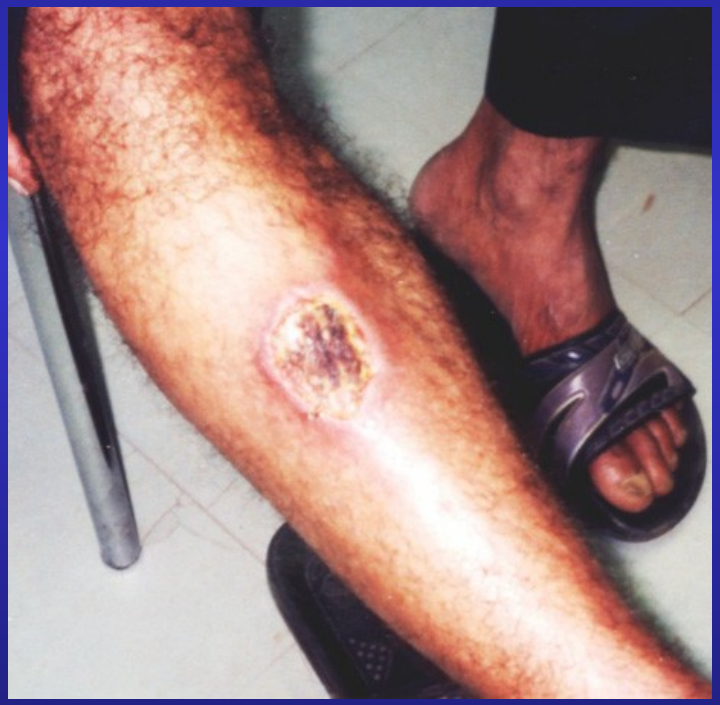
Work Up



- History and physical
- Visualization and culture
- Montenegro Skin Test
  - similar to PPD
  - not standardized
  - made from killed promastigotes

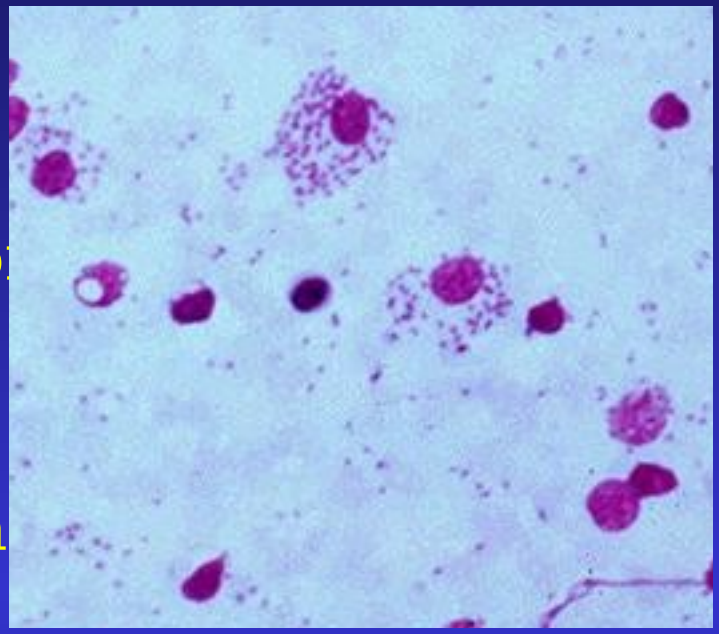
Biopsy

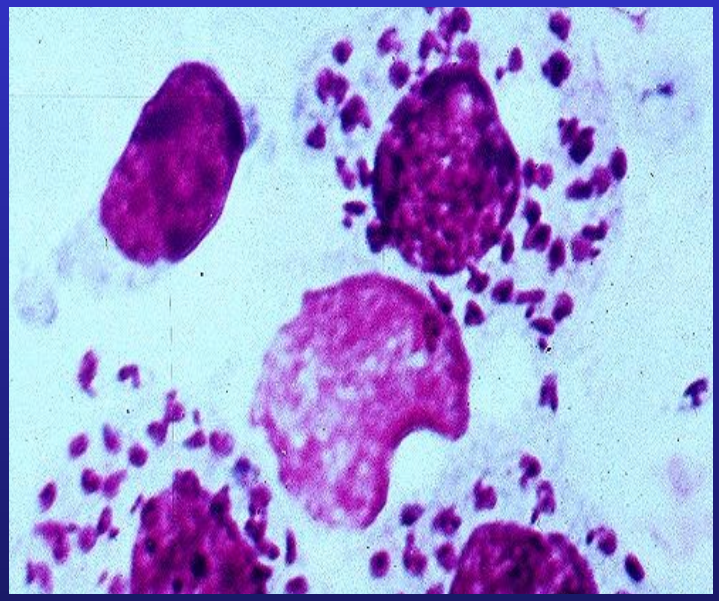
- Cutaneous
  - Punch biopsy
  - Avoid necrotic center
- Mucocutaneous
  - Mucosal granuloma biopsy
  - Difficult to isolate
- Visceral
  - Bone marrow
  - Splenic aspiration
  - Contraindications
    - platelets
    - prothrombin time
    - non-palpable spleen

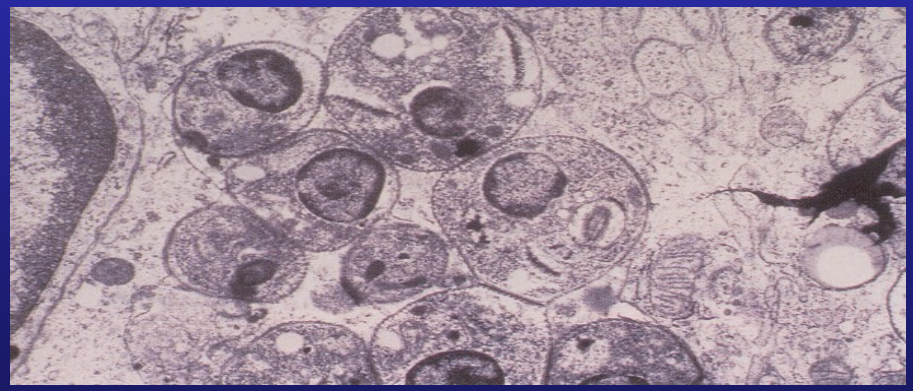


Biopsy

- Send for:
  - Touch preparations
  - Formalin-fixed paraffin sectio
- Staining:
  - Hematoxylin and eosin
  - Geimsa for touch preps and a
- Exam for:
  - Amastigote in macrophages

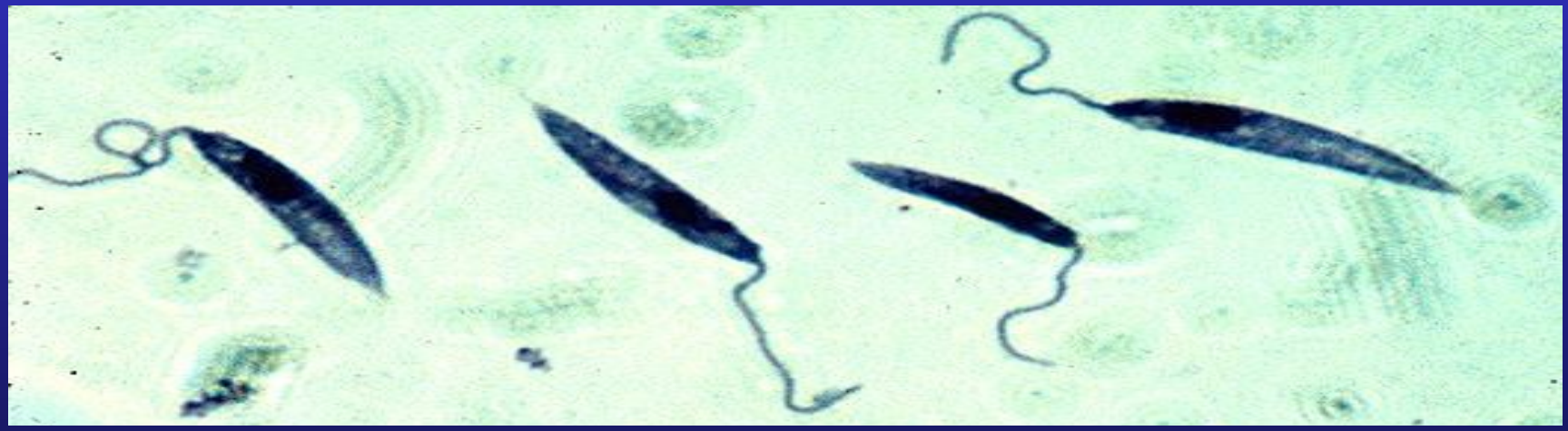






Culture

- Medium to
  - NNN
  - Rabbit Blood Agar
  - Schneider's Drosphilia
- Positive cultures in 24 hours to weeks
- Able to culture organisms 75% of time



Additional Tests

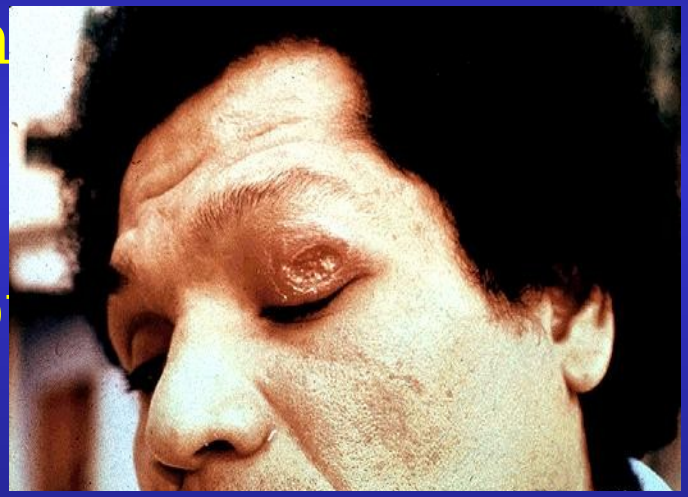
- ELISA and direct agglutination test
- Monoclonal antibody immunofluorescence
- PCR
  - Currently being developed at WRAMC
- Rapid diagnostic antibody dipsticks
  - Quick test for visceral dise

Labs

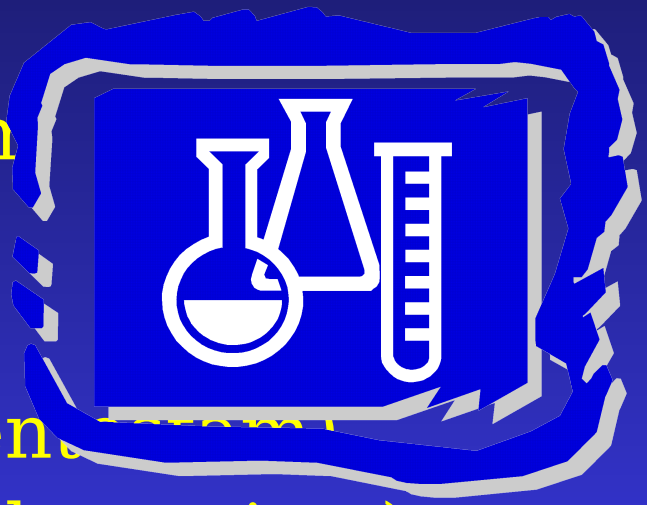
- Cutaneous/Mucocutaneous
  - normal labs
- Visceral
  - CBC
    - Anemia
  - SPEP
    - Spike
  - LFTs
    - Mild elevations
  - Coag panel

Treatment

- Decision to treat
  - Treat visceral and mucocutaneous
  - Treat New World cutaneous disease
  - Old World cutaneous disea
    - Tends to resolve
    - Treat if:
      - Cosmetically unaccep
      - Painful
      - Infected
      - Species dependant



Pentavalent Antimony Compounds



- Not FDA approved
- Poorly understood mechanism of action
- Two available compounds
  - Sodium Stibogluconate (Pentostam)
  - Meglumine Antimoniate (Glucantime)
- Available from the CDC and WRAMC
- Therapy
  - Expensive
  - Need prolonged treatment
  - Some side effects

Sodium Stibogluconate (Pentostam)

- Dose
  - Cutaneous: 20mg/kg IV QD for 20 days
  - Mucocutaneous: 20mg/kg IV QD for 28 days
  - Visceral: 20mg/kg IV QD for 28 days
- Side effects
  - 94% chemical pancreatitis
  - 63% elevated LFTs
  - 58% severe arthralgias/myalgias
  - 31% gastrointestinal distress
  - 27% EKG changes
- Discontinue therapy if:
  - QT interval >0.5, Use frequent EKG monitoring
  - LFTs and amylase >5 times upper limit
  - Lipase >15 time upper limit
- Prior to therapy
  - EKG, serum electrolytes, LFTs, amylase, lipase, CBC, BUN and creatinine

Second Line Therapies

- Amphotericin B
  - Effective against resistant disease
  - Toxic side effects
  - Lipid formation better tolerated
  - High relapse rate
- Pentamidine
  - Effective against visceral disease
  - Associated with persistent diabet
  - High relapse rate

Second Line Therapies

- Oral medications
  - Ketoconazole, itraconazole, fluconazole, allopurinol and dapsone
- Topical
  - Paromycin effective against cutaneous disease
  - Not licensed in the U.S. but currently used by Israeli army

New Therapies

- Miltefosine
  - Recent phase 2 drug study
  - Showed orally administered miltefosine was 95% effective
  - Phosphocholine analogue
  - Treat four to six weeks
  - Mild side effects :

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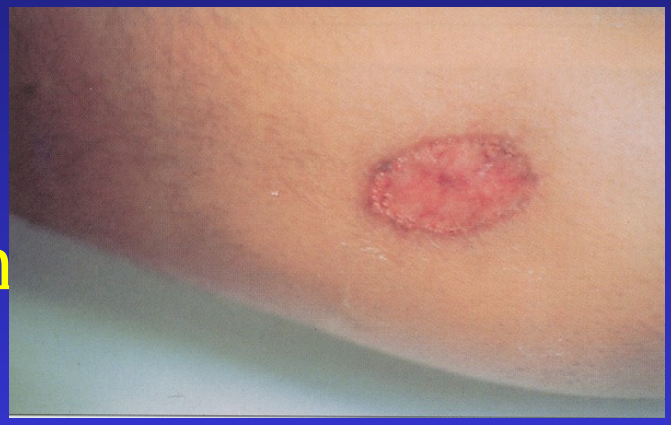
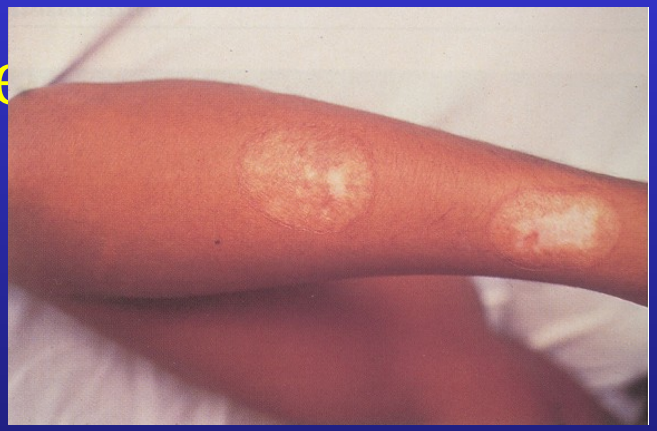
Further Care

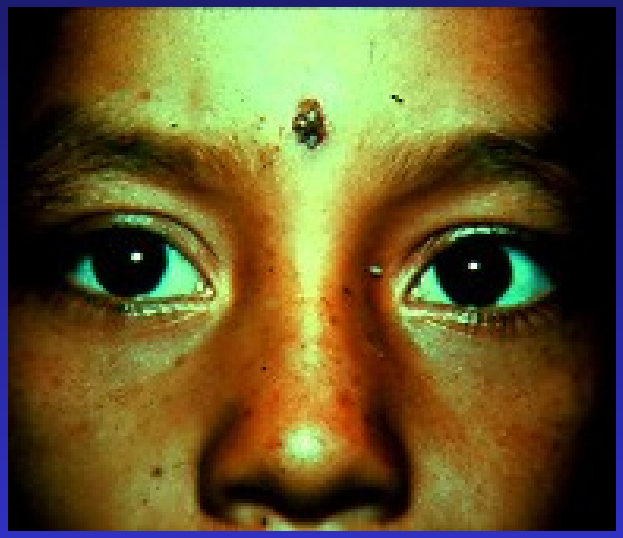
- Prognosis
- Supportive care
- Treat bacterial infections
- Follow up in 6 weeks after th
  - Cutaneous disease
  - Visceral disease
- Retreatment with second line
  - for resistant disease
  - for reinfection

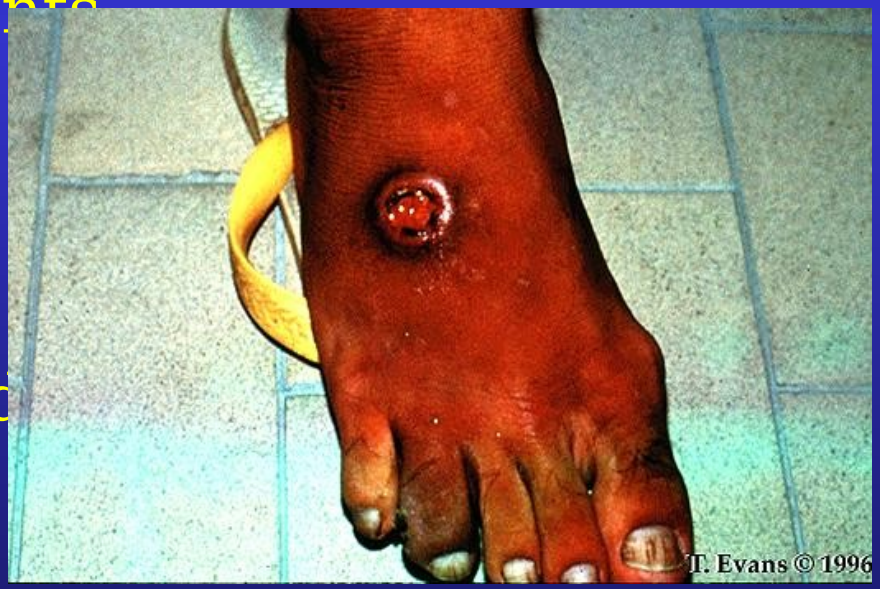




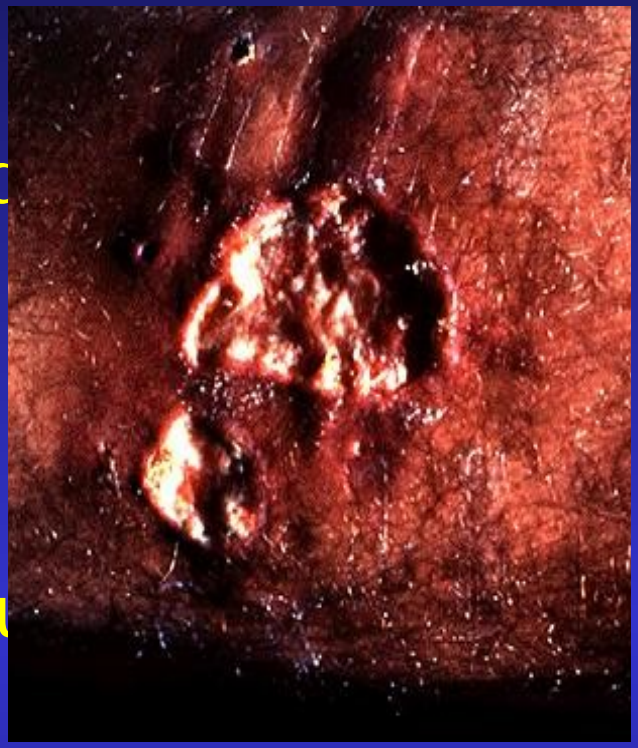
Prevention

- Vaccine trials
  - No approved vaccine
- Limit disease by
  - Reservoir eradication
  - Vector control
  - Mass treatment of patients
- Personal prevention
  - Insect repellent
  - Protective clothing
  - Permethrin-impregnated





Conclusions



- Increasing incidence worldwic
- Military specific disease
- Local disease may progress
- Visceral disease is fatal
- Diagnose by staining and cultu
- Species ID important
- Treatment with pentavalent antimonal
- Lipid Amphotericin B second line drug
- Prevention

Questions??